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RESEARCH ARTICLE

Effect of Herbal *Ephedra sinica* and *Evodia rutaecarpa* on Body Composition and Resting Metabolic Rate: A Randomized, Double-blind Clinical Trial in Korean Premenopausal Women

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Abstract

Background: As obesity is becoming an epidemic, diet programs, including low-calorie diets, are continuously being developed. It is generally believed that a low-calorie diet is commonly followed by a resting metabolic rate decrease and ultimate weight regain. *Ephedra sinica* and *evodia rutaecarpa* are known to have sympathomimetic and anti-obesity effects.

Design and Objective: This study was a prospective; double-blinded, randomized and placebo-controlled clinical trial to evaluate the effects of *ephedra sinica* and *evodia rutaecarpa* on resting metabolic rate (RMR), body composition and short-term safety in obese Korean premenopausal women on a low-calorie diet.

Methods: One hundred and twenty-five otherwise healthy obese women (body mass index $\geq 25\,kg/m^2$) were recruited and randomly assigned to three groups: ephedra group ($n=41$), evodia group ($n=45$) and placebo group ($n=39$). Subjects were administered ephedra extract in capsules (pseudo-ephedrine 31.52 mg) or evodia extract in capsules (evodiamine 6.75 mg, rutaecarpine 0.66 mg) or placebo capsules as well as participating in a low-calorie diet for 8 weeks. Resting metabolic rate and body composition were measured at baseline, 4 and 8 weeks. Basic serum tests were performed to evaluate the short-term safety and lipid-lowering effects of the herbs.

Results: All three groups showed significant body mass index (BMI) decreases, probably due to the low-calorie diet. Among the groups, the most prominent BMI-reducing effect was seen in the ephedra group. In RMR, no significant change in any group or significant difference among the groups was found. No significant adverse effects were observed in serum tests or in the self-questionnaire.

Conclusion: Ephedra combined with a low-calorie diet was effective in reducing BMI. RMR change was not compensated for by the herbal medicines tried. RMR change seemed to be affected by constitution and body composition rather than by medicine. Ephedra and evodia were proven to be safe for short-term use in the herbal form.

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1. Introduction

The rising prevalence of obesity in the last 20–30 years has led to obesity being characterized as an epidemic. The World Health Organization announced that obesity and its complications are the leading world-wide health threat [1]. Although numerous weight loss programs have been developed in conventional medicine, their effectiveness has proven to be quite limited [2]. Meanwhile, alternative agents, including herbs used in Chinese medicine, have been consumed extensively in the United States and European countries for weight loss purposes. Among these agents, preparations that include ephedra are the most popular [3].

Ephedra is the stem of *ephedra sinica*, also known as *ma-huang*, and has been used in Chinese medicine for over 5000 years as a treatment for the common cold, arthralgia, asthma and other ailments [4,5]. Because of its sympathomimetic effect, various herbal mixtures containing ephedra have been used for obesity treatment in western countries as well as in Asia.

The fruit of *evodia rutaecarpa* is regarded as a 'hot nature' herb in Chinese literature. Evodiamine is a major component of the herb and manifests capsaicin-like vanilloid receptor agonist activity [6,7]. Some studies have reported that capsaicin and evodia have anti-obesity effects [6].

Energy expenditure is commonly divided into three components: resting metabolic rate (RMR), physical activity and thermogenesis induced by food intake, exposure to cold, and other stressors. RMR accounts for the largest proportion (60–75%) of total daily energy needs in individuals, but the contribution of a low RMR to the etiology of obesity is still controversial [1,8]. However, it is well established that energy restriction and weight loss may cause a sustained suppression of the RMR for a given body composition [1]. The decreased RMR may be important for weight regain in obese subjects after weight loss during a diet program [9]. Therefore, clinicians involved in bariatric management have a great interest in keeping or enhancing the RMR of patients during a low-calorie diet.

In the present study, the authors hypothesized that the RMR decline, which may be a major factor for weight regain during a diet program, can be minimized by the metabolism promotion effect of ephedra and evodia, and that both herbs have some effects on body composition. The short-term safety of using ephedra and evodia was also evaluated by the means of blood chemistry and self-questionnaire.

2. Methods

2.1. Study design

The present study was a randomized, controlled, double-blind clinical trial to assess the efficacy and safety of herbal extracts of *ephedra sinica* and *evodia rutaecarpa*, and was conducted in Bundang CHA Hospital, South Korea for 8 weeks between December 2004 and May 2005.

A total of 142 women volunteered for the study by e-mail. Seventeen were not selected due to possible health hazards or incorrect body mass index (BMI; under 25 kg/m^2). The remaining 125 volunteers had blood exams in the main laboratory of CHA Hospital on the first visit. The subjects, healthy Korean premenopausal women, were assigned to three groups of ephedra, evodia and placebo by randomization. Randomization was conducted by choosing a number from 1 to 125 already randomly allotted to three groups by randomization computer software. 41, 45 and 39 subjects were thus allotted to the ephedra, evodia, placebo groups, respectively. The study was blinded for all researchers involved.

After assignment, subjects were educated on a healthy low-calorie diet of 1200 kcal/day. A diet diary was encouraged during the whole study period to check dietary compliance. Moderate exercise (40 minutes walk, five times in a week, 70% of maximum heart rate) was indicated. All other medicines, diet or exercise programs were prohibited during the study. After instruction, subjects were given a 4 week supply of herbal extract capsules in an opaque bottle. Unconsumed capsules were

Table 1 Evaluation progress

	1st visit	2nd visit Week 0	Week 2	3rd visit Week 4	Week 6	4th visit Week 8
Body composition		✓		✓		✓
Metabolic rate		✓	Telephone	✓	Telephone	✓
WHR		✓	counsel	✓	counsel	✓
Blood sampling	✓					✓

returned to the pharmacist after 4 and 8 weeks, and subjects who had not taken 2/3 of their capsules were excluded from the study. On the second visit, resting metabolic rate, body composition and basic anthropometric parameters were measured. Between visits, a researcher contacted subjects by telephone to check on the diet program and remind them of the next scheduled visit. After 4 weeks and 8 weeks, the third and fourth visits were made to reexamine the resting metabolic rate, body composition and basic anthropometric parameters. A follow-up blood exam was only done at week 8 (Table 1). Blood pressure was measured on the first and last visits. To evaluate adverse effects of both herbs, symptoms and signs were self-reported before and after the experiment.

Prior to the experiment, the basic purpose and principle of the study, potential adverse effects of herbal extracts as well as their right of withdrawal from the study was thoroughly explained to all subjects, and subjects were asked to sign a personal consent form. The study was approved by the Institutional Review Board of Bundang CHA Hospital.

2.2. Subjects

Subjects were recruited by advertisements in local newspapers and on the webpage of Bundang CHA Hospital. To qualify, subjects needed to be premenopausal Korean women between 21 and 50 years of age and have a BMI over 25 kg/m^2 and must have been weight-stable within ± 3 kg during the previous 6 months. Only non-smoking, moderately sedentary housewives and office-workers who did not exercise regularly and walked less than 30 minutes a day were recruited. Volunteers applied to the trial by e-mail and were screened by a researcher. A physician interviewed the volunteers on their general health. Women with a past history of cardiovascular disease, renal or hepatic dysfunction, cancer, neurological or psychological illness or metabolic disease were excluded from the study. Any subject taking drugs that could affect metabolic rate was also excluded. Pregnancy at any time during the study was among the exclusion criteria.

During the study, subjects who did not keep to the recommended dietary program, moved to another city or traveled abroad or who manifested adverse effects of the drugs were dropped from the study. Also 26 subjects in the first 4 weeks and 16 others in the last 4 weeks abandoned the program out of personal choice. In week 8, 57 subjects completed the study: 21 from the ephedra group, 20 from the evodia group and 16 from the placebo group.

2.3. Preparation

Evodia and ephedra used in the study were obtained from the Department of Oriental Pharmacology at Bundang CHA Hospital (Bundang, Korea). After washing, each herb was hot water-extracted at 105°C for 70 minutes. The herbal solution was concentrated in a decompressed condition at 60°C. To obtain the powder extract, the solution was spray-dried. The herb powder was contained in 250 mg capsules. Subjects were ordered to take four capsules 30 minutes after each meal, three times a day, for a total of 12 capsules a day. The recommended maximum daily doses of ephedra and evodia in natural herb form are 12 g according to the Korean Oriental Association for the Study of Obesity. The effective acquisition rates of extraction in the study were 17.4% and 24.9% in ephedra and evodia, respectively. Therefore, roughly 3 g of evodia (evodiamine 6.75 mg, rutaecarpine 0.66 mg) extract powder and 2 g of ephedra (pseudoephedrine 31.52 mg) extract powder were equivalent to 12 g of natural herbs. One gram of corn starch was added to the ephedra powder to make the amount identical to the evodia powder. The placebo contained 3 g of corn starch in a capsule of identical appearance.

2.4. HPLC analysis of standard materials to test samples

The Laboratory of Oriental Pharmacology, Oriental Medical Hospital, KyungHee University, Seoul, Korea, analyzed the samples of the herbal extracts by high-performance liquid chromatography (HPLC).

The hot water-extracted ephedra and evodia powder, each accurately weighed to 1 g, were put in a test tube and dissolved in 10 mL of 100% ethanol for the pseudoephedrine content of ephedra, in 10 mL of methanol (HPLC reagent, J.T. Baker Co. Ltd., NJ, USA) for the evodiamine content of evodia and 10 mL of chloroform-acetonitrile mixed solution (1:1, v/v) for the rutaecarpine content of evodia. Filtering through a 0.45 μm syringe filter (PTFE, Waters, MA, USA) followed. Each marker substance (standard materials) used for the quantitative analysis was purchased: pseudoephedrine (Sigma-Aldrich, St. Louis, MO, USA), evodiamine (Wako Pure Chemicals India Ltd., Osaka, Japan), and rutaecarpine (Sigma-Aldrich, St. Louis, MO, USA).

Each standard material was dissolved in the same reagent with the corresponding sample solution. The dissolved standard solution was diluted as 0.05, 0.1, 0.25, 0.5 and 1.0 mg/mL, and the standard HPLC chromatogram obtained. The relationship between the concentration and the peak-area was measured by a minimum square method (R^2 value) [10]. The HPLC apparatus was a Waters Breeze System

(717+Autosampler, 2487 dual absorbance detector, 1525 binary HPLC Pump, Waters Co., Milford, USA). Waters Empower System (Ver. 5.00) was used for data acquisition and integration. The quantities of standard materials contained in the sample powder were calculated by the following formula: the amount (mg) of standard materials = [the quantitative amount (mg) of standard materials *AT/AS]/n where $n = 3$, AT = the peak-area of test samples containing standard materials and AS = the peak area of standard materials.

From the results of the standard calibration curve, R^2 values of pseudoephedrine, evodiamine and rutaecarpine were 0.997, 0.997 and 0.998, respectively.

2.5. Evaluation

2.5.1. Resting metabolic rate

An indirect calorimeter (MedGem, Healthetech, USA) was used for the measurement of RMR. This hand-held device was comprised of a mask and the cylinder-shaped main unit with an LCD-indicator. The mask covered the nose and mouth and was connected to the main body. This calorimeter unit was auto-calibrated prior to each test. The subjects breathed normally through the mask for 12 minutes whilst sitting in a comfortable seat with their elbows propped against an armrest. To maximize the accuracy, all subjects were requested to fast for at least 2 hours and to rest in a quiet place of room temperature and humidity for at least 20 minutes. Because the menstrual period of subjects can affect the RMR, the examination date was scheduled during the follicular phase, which follows menstruation by approximately 2 weeks. Oxygen concentration in the inspired and expired airflow was measured by an authentic sensor. RMR is calculated from oxygen consumption and displayed on LCD in kcals/day at the conclusion of the test.

2.5.2. Anthropometry and body composition

While they were wearing a hospital gown, participants' body weight and height were measured to the nearest 0.1 kg and 0.5 cm respectively. The waist circumference and waist-to-hip ratio (WHR) were measured twice according to the WHO method by the same observer.

On the second visit, body composition was measured by the bioelectrical impedance analysis method (InBody 3.0, Biospace, Korea). This device measures the impedance through the eight tactile electrodes placed on palms, thumbs, heels, and soles. Each subject stood upright stepping onto the foot electrodes whilst loosely gripping the pipe-shaped hand electrodes with arms held vertically. Lean body mass, body mass index and percent fat were measured and recorded. Follow-ups were made 4 and 8 weeks later.

2.5.3. Blood chemistry

Blood tests including fasting glucose, blood urea nitrogen (BUN), creatinine, high density lipoproteins (HDL)-cholesterol, triglyceride, total cholesterol, aspartate aminotransferase/alanine aminotransferase (AST/ALT), C-reactive protein, platelet count, red and white blood cell count, hemoglobin, hematocrit and mean cell volume were carried out before the experiment and 8 weeks later to ensure the safety of the herbal medicines and examine the effect on the lipid profile. At the baseline, subjects with high fasting blood glucose (>140 mg/dL) or possible liver problems (AST or ALT >80 IU/L) were excluded. No other serious illnesses were found at the baseline blood test.

2.6. Data analysis

All results are expressed as mean ± SD. All analyses were conducted at the two-tailed 0.05 alpha level using SPSS 10.0 for Windows. General characteristics among the groups were analyzed by means of analysis of variance (ANOVA) and chi-square test. A one-way repeated measures ANOVA (Scheffe's post hoc) was used to compare the pattern of change of RMR, body composition parameters and blood profiles among the groups over 4 and 8 weeks. Linear regression analysis was performed to get equations and to evaluate the correlations between RMR change and other parameters.

3. Results

3.1. Study progress

125 subjects were randomized after 17 dropouts. During the first 4 weeks the ephedra, evodia, and placebo groups experienced 14, 19, and 16 subject, respectively. These were mostly due to transfer or personal choice (Figure 1). At the fourth week, 27, 26 and 23 remained in each group, followed by another six, six and seven dropouts respectively. At the last visit, 21, 20 and 16 subjects appeared and completed the study.

3.2. General characteristics of subjects

Among the three study groups, age, weight, RMR, WHR, fat free mass, fat percentage, serum cholesterol and serum triglyceride were not different

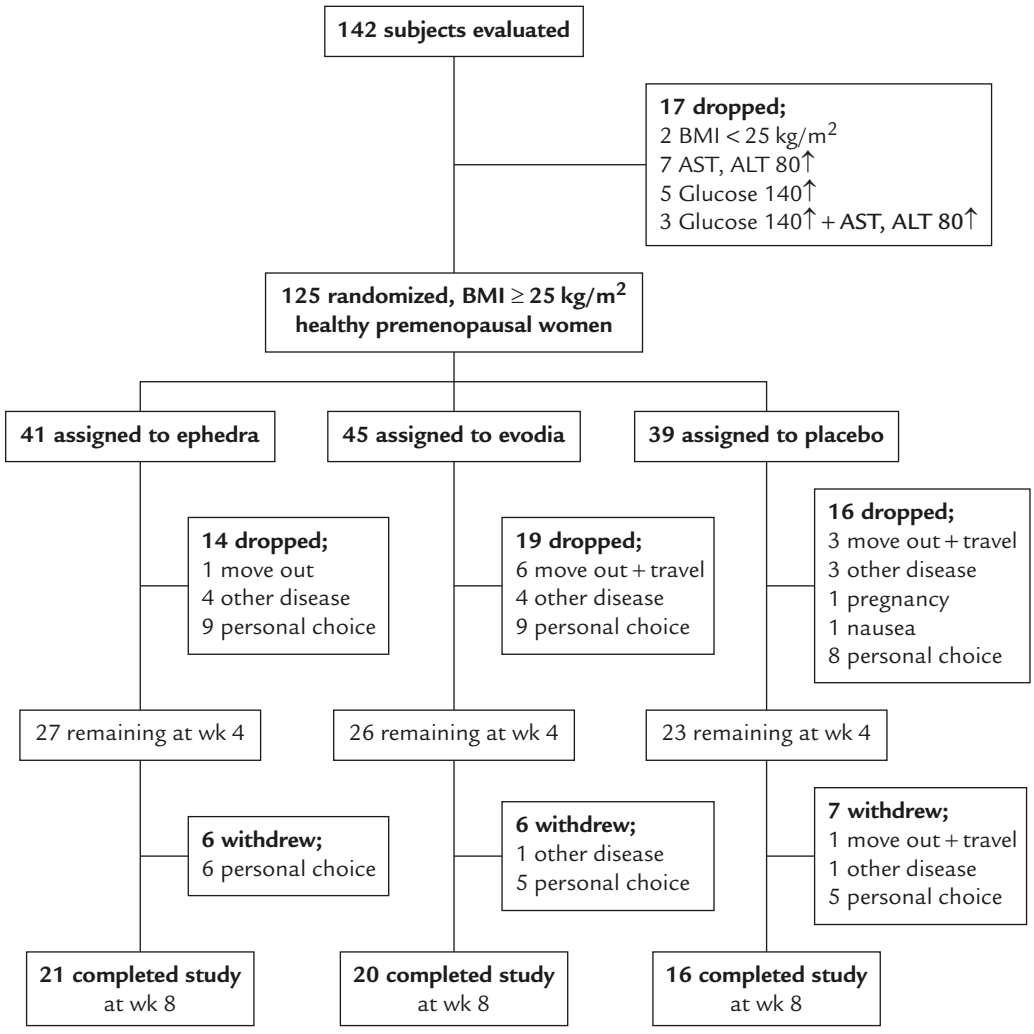

Figure 1 Process and condition of each group. BMI = body mass index.

Table 2 Subjects' baseline assessment

	Ephedra group (n=21)	Evodia group (n=20)	Placebo group (n=16)	p*
Age (yr)	33.8±7.9	34.8±6.4	30.8±7.4	N.S.
Body mass index (kg/m^2)	27.4±2.3	29.1±2.9	27.9±2.0	N.S.
Resting metabolic rate (kcal/d)	1481.7±224.4	1593.5±301.9	1563.8±289.7	N.S.
Waist to hip ratio	0.91±0.05	0.92±0.07	0.90±0.04	N.S.
Percent body fat (%)	36.0±4.0	37.1±3.5	36.1±3.3	N.S.
Fat free mass (kg)	43.9±3.6	46.7±4.0	47.5±5.0	0.016
Total cholesterol (mg/dL)	194.3±25.7	174.9±29.1	178.5±22.3	0.039
Triglyceride (mg/dL)	138.3±74.0	130.0±76.4	121.3±47.9	N.S.
Blood pressure, mmHg (systolic/diastolic)	114.0±11.7/ 75.6±7.7	115.6±10.9/ 79.4±9.3	122.0±11.9/ 84.5±12.3	0.017

*Analyzed by ANOVA for continuous variables and Chi-square test for categorical variables.

statistically at the baseline (p>0.05). Initial blood pressures between the ephedra and evodia groups were statistically different from each other (p<0.05, Table 2).

3.3. Herbal analysis

The extracted ephedra powder contained 15.76 mg of pseudoephedrine in one gram of extracted ephedra

Table 3 The quantitative analysis results of the ephedra and evodia by HPLC

Sample	(+)-Pseudoephedrine	Evodiamine	Rutaecarpine
Ephedra sinica	15.76±5.44	–	–
Evodia rutaecarpa	–	2.25±0.46	0.22±0.02

unit = mg/dried ex. g

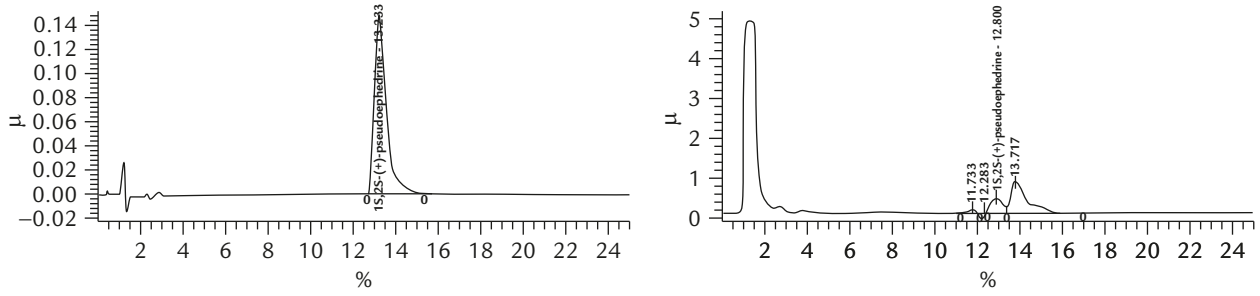

Figure 2 HPLC chromatogram of (+)-pseudoephedrine from the standard material (Lt) and from ephedra extract (Rt).

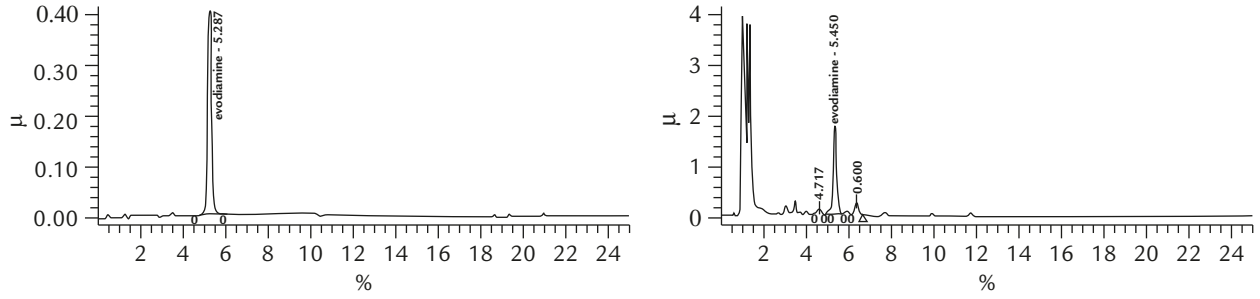

Figure 3 HPLC chromatogram of evodiamine from the standard material (Lt) and from evodia extract (Rt).

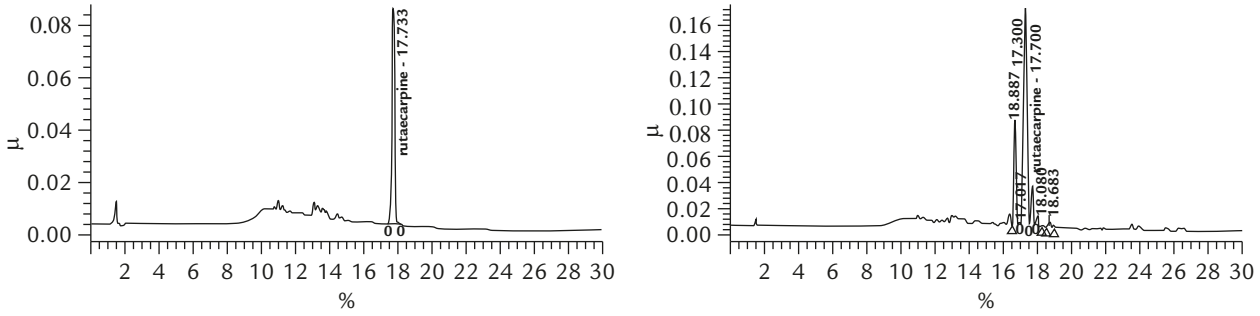

Figure 4 HPLC chromatogram of rutaecarpine from the standard material (Lt) and from evodia extract (Rt).

powder, while in one gram of evodia extract, 2.25 mg of evodiamine and 0.22 mg of rutaecarpine were included (Table 3). Chromatograms of standard materials and a sample extract of pseudoephedrine (Figure 2), evodiamine (Figure 3), and rutaecarpine (Figure 4) are shown.

3.4. Body composition and RMR

The longitudinal changes of body composition parameters and RMR at weeks 0, 4, and 8 as well as cross-sectional comparison among groups are shown in the Table 4.

All three groups showed significant weight and BMI decreases. Among the groups, the ephedra group manifested the most prominent weight-reducing effect. The ephedra group showed a significant reduction of body weight compared with the evodia and the placebo groups in weeks 4 and 8. However, we could not find any significant RMR change. The waist-hip ratio was significantly changed in the ephedra ($p<0.01$) and placebo groups ($p<0.05$).

Table 4 Changes of the body composition parameters

	Ephedra group (n=21)	Evodia group (n=20)	Placebo group (n=16)	p*
Resting metabolic rate (kcal/d)				
Baseline	1481.7±224.4	1593.5±301.9	1563.8±289.7	N.S.
After 4 wks	1483.8±300.8	1568.5±291.6	1597.5±296.5	N.S.
After 8 wks	1405.0±265.4	1524.0±289.6	1646.3±359.5	N.S.
Body mass index (kg/m^2)				
Baseline	27.4±2.3	29.1±2.9	27.9±2.0	N.S.
After 4 wks	26.4±2.3‡	28.4±2.9‡	27.3±2.2‡	0.035
After 8 wks	25.7±2.1‡	28.0±3.2‡	27.3±2.5†	0.020
Waist to hip ratio				
Baseline	0.91±0.05	0.92±0.07	0.90±0.04	N.S.
At wk 4	0.90±0.05‡	0.92±0.05	0.89±0.04†	N.S.
At wk 8	0.88±0.05‡	0.91±0.05	0.89±0.04†	N.S.
Percent body fat (%)				
Baseline	36.0±4.0	37.1±3.5	36.1±3.3	N.S.
At wk 4	34.9±4.1‡	36.4±3.9‡	35.5±3.4‡	N.S.
At wk 8	33.7±4.0‡	36.0±3.9‡	35.2±3.9†	N.S.
Fat free mass (kg)				
Baseline	43.9±3.6	46.7±4.0	47.5±5.0	0.030
At wk 4	43.0±3.6‡	46.2±4.3	47.1±4.8	0.015
At wk 8	42.5±3.5‡	45.8±4.3	47.2±5.1	N.S.

*Analyzed by one-way ANOVA between groups; †$p<0.05$ and ‡$p<0.01$ *vs.* baseline by paired t-test, respectively.

Table 5 Association between subject characteristics and RMR change by multiple regression analysis

	Model 1 (adjusted R^2=0.272) B coefficient (Sig.)	Model 2 (adjusted R^2=0.272) B coefficient (Sig.)
Age (yr)	0.6 (0.920)	
Ephedra group	Reference	
Evodia group	65.9 (0.425)	
Placebo group	108.1 (0.228)	
Body mass index (kg/m^2)	−113.2 (0.007)	−87.7 (0.002)
Baseline RMR (kcal/d)	−0.5 (0.001)	−0.6 (<0.001)
Waist to hip ratio	1451.6 (0.124)	
Percent body fat (%)	47.5 (0.025)	49.1 (0.003)
Fat free mass (kg)	43.4 (0.006)	43.0 (0.001)

Model 1 included all of the assessed variables and Model 2 included only significant variables which remained after backward method.

No significant difference of WHR between groups was observed at weeks 0, 4 and 8. The percent of body fat was significantly decreased in all three groups. However, no significant inter-group difference was found in percent body fat. While the fat free mass was preserved during 8 weeks in the evodia and placebo groups, the ephedra group showed a significant decrease.

Multiple regression analysis of 57 subjects regardless of groups was performed to investigate the relationship between RMR change and other variables (Table 5). The age, herbs administered and WHR showed no significant influence to the change of RMR. On the other hand, the percent of body fat and the fat free mass showed a positive correlation to the change of RMR, while BMI and baseline RMR proved to be correlated negatively.

3.5. Blood chemistry

The results of the serum test are shown in Table 6. At baseline, there was significant difference between

Table 6 Changes of the laboratory findings after treatment

	Ephedra group (n=21)	Evodia group (n=20)	Placebo group (n=16)	p*
Aspartate transaminase (U/L)				
Baseline	17.7±4.1	16.7±3.8	18.0±5.2	N.S.
After 8 wks	15.5±3.0†	20.0±8.1	17.0±4.5	N.S.
Alanine transaminase (U/L)				
Baseline	18.0±8.7	19.0±5.8	19.3±10.2	N.S.
After 8 wks	15.5±7.9	24.3±14.9	15.7±6.6	0.016
Blood urea nitrogen (mg/dL)				
Baseline	13.2±3.4	11.7±3.5	10.6±2.8	0.041
After 8 wks	11.8±2.8	10.6±2.8†	11.1±2.3	N.S.
Creatinine (mg/dL)				
Baseline	0.78±0.08	0.78±0.12	0.75±0.08	N.S.
After 8 wks	0.80±0.09	0.78±0.14	0.77±0.10	N.S.
Total cholesterol (mg/dL)				
Baseline	194.3±25.7	174.9±29.1	180.4±21.7	0.039
After 8 wks	170.1±23.9‡	176.4±34.2	173.7±28.7	N.S.
Triglyceride (mg/dL)				
Baseline	138.3±74.1	130.0±76.4	122.9±49.2	N.S.
After 8 wks	100.3±56.3†	111.4±43.4	114.8±55.0	N.S.

*Significance was calculated by one-way ANOVA, and Scheffe's post hoc test revealed $p<0.05$ in the difference between the maximum value and the minimum value; †$p<0.05$ and ‡$p<0.01$ *vs*. baseline by paired t-test, respectively.

groups only in BUN. In the variables for drug safety, decreases of AST in the ephedra group and BUN in the evodia and the ephedra groups were observed. Lipid profiles including total cholesterol and triglyceride were significantly improved in the ephedra group. All of the mean values are within the reference ranges.

3.6. Adverse effects

Subjects were required to fill out the self-questionnaire about adverse events due to the herbs at 0, 4, and 8 weeks. In the ephedra group, when compared with the baseline, palpitation, insomnia, dry mouth and gastrointestinal symptoms such as anorexia, nausea, vomiting, and constipation were increased at week 8. Although incidence was lower in the ephedra group, the evodia group also showed increases of symptoms including palpitation, trembling, dizziness, nervousness, gastrointestinal symptoms etc. The placebo group complained of increased insomnia and eruption (Table 7).

4. Discussion

The main purpose of the present study was to prove that *ephedra sinica* and *evodia rutaecarpa* have anti-obesity effects in terms of the resting metabolic rate and body composition as well as showing that they are safe enough for short-term use during a low-calorie diet.

The resting metabolic rate (RMR) comprises 50–80% of daily energy expenditure, and is highly variable between subjects. This variability is related to differences in fat free mass, fat mass, age and sex. RMR is believed to be genetically determined. Individuals with a low RMR are at higher risk of significant weight gain, relative to those with a high RMR [1,9].

The accurate assessment of RMR requires sophisticated methodologies. These include the use of human calorimeters, closed-circuit and open-circuit indirect calorimetry equipment such as Douglas bags and gas analyzers and whole body respiratory chambers [8]. However, in the present study, a handheld indirect calorimeter was used. This device proved to be reliable when compared with the classic Douglas bag method [8].

Energy restriction and weight loss may cause a sustained suppression of the RMR for a given body composition. The suppression of RMR may be important for understanding the high rate of weight regain in obese subjects after weight loss. According to the analysis of Astrup [1], formerly obese subjects had a 3–5% lower RMR than never-obese control subjects. In addition, a larger proportion of the formerly obese subjects had a low RMR (15.3% compared with 3.3%).

Table 7 Adverse effects in the three groups for 8 weeks

	Ephedra (n=21)			Evodia (n=20)			Placebo (n=16)		
	Wk 0	Wk 4	Wk 8	Wk 0	Wk 4	Wk 8	Wk 0	Wk 4	Wk 8
Palpitation	0	1	1	0	1	1	0	0	0
Headache	7	5	7	3	1	2	2	1	0
Dull head	8	3	4	2	1	2	3	0	0
Tremble	0	1	0	0	0	1	1	1	0
Insomnia	0	3	4	2	2	2	1	0	2
Dizziness	4	5	4	2	1	3	4	1	0
Nervousness	2	0	1	0	0	1	2	1	1
Nausea	0	2	2	0	0	0	0	1	0
Vomiting	0	3	2	0	1	1	0	0	0
Anorexia	0	3	1	0	1	1	0	0	0
Constipation	8	11	12	3	1	4	4	6	3
Dysuria	0	0	0	0	0	1	1	1	0
Eruption	0	0	0	0	0	0	0	0	1
Dry mouth	0	5	6	0	1	1	1	1	1
Breathlessness	0	1	0	0	0	0	0	0	0

In order to minimize the RMR decrease during calorie-restricted diet, numerous medical methods have been designed. Exercise added to a diet program seems to maintain lean body mass, a condition which may prevent a decline in RMR [11]. In addition, sympathomimetic agents are prescribed to compensate for RMR decrease. On the other hand, herbal anti-obese products are obtaining increasing worldwide popularity because of their easy accessibility and apparent safety. Among several commercialized herbs with sympathetic stimulating effects, ephedra is one of the most popular [3].

Ephedra sinica contains 1–2% alkaloids composed of ephedrine and pseudoephedrine. The main component ephedrine has been called an "energizer" for stimulating the central nervous system and the heart, increasing the heart rate and often elevating blood pressure. Although its anti-obesity effect through fat-burning and appetite-suppression is not fully approved, it is a common ingredient in many weight loss and energy-enhancing products [12,13].

Several studies have already combined a low-calorie diet with ephedra or ephedrine. Malchow-Moller et al reported that a low-calorie diet with ephedrine (180 mg/day) and caffeine (600 mg/day) group showed a significant weight loss of 4.0 kg compared with a placebo group [14]. Boozer et al also demonstrated an herbal supplement containing *ma-huang* (72 mg/day ephedrine) and guarana was significantly effective in weight reduction in an 8-week controlled trial [3].

In the present study, although the evodia and placebo groups also showed a significant weight-reducing effect at weeks 4 and 8, ephedra was the most effective herb. The WHR reduction was also most obvious in the ephedra group, although no significant difference among groups was observed. In Astrup's study [15] with ephedrine and caffeine, a significant body composition benefit was found; more fat loss, less fat-free mass loss. In the present study, although we also observed a distinct percent body fat decrease—meaning relatively greater fat mass reduction than fat free mass—in the ephedra group, no statistical significance among groups was found.

Several sympathomimetic agents has been tried to elucidate their pharmacological mechanism in terms of metabolic rate. Sibutramine [16], phenylpropanolamine [17] and phentermine [18] were tried to assess RMR-promoting and weight-reducing effects. Despite significant weight loss and anorexic effects, they failed to demonstrate the drugs' mechanism as RMR-promoters. In a clinical trial with ephedra, Vukovich demonstrated an acute dose of the herb combined with caffeine increased resting energy expenditure (REE) by 8.5% compared with the placebo trial [19]. However, the author emphasized that although significant, the increase in energy expenditure is negligible in terms of weight loss. Another study of Greenway also showed 8% of RMR increase in an ephedra with caffeine group when measured after 2 hours of administration. Beyond the acute effect, there is Astrup's study [15]. The ephedra with caffeine group showed significantly less decrease of 24-hour energy expenditure compared with placebo after 8 weeks of an energy restricted diet.

In the present study, however, the authors failed to prove that ephedra has any chronic RMR-promoting effect during the 8-week low-calorie diet. An acute RMR-promoting effect was not evaluated in the

present study. We suppose the weight reduction does not seem to be affected by RMR promotion.

To elucidate which parameter most affected the change of RMR, multiple regression analysis was performed. The result showed that body composition most influenced the change of RMR. In particular, higher lean body mass and percent body fat can predict more change in RMR while a higher BMI and baseline RMR can be interpreted as factors for a more stable RMR. On the other hand, no herb affected RMR change significantly. This analysis signifies that body composition, closely associated with genetic factor, as asserted in Astrup's study [1], is more important to predict RMR change during an energy-restricted diet.

Evodia has been prescribed for the treatment of headache, thoracicoabdominal pain and vomiting that are caused by 'cold', or 'cold constitution' in Oriental medicine because of its 'hot nature'. Several animal studies about evodia were focused on the cardiotonic, broncho-constrictive effect possibly associated with the vanilloid receptors of evodiamine [7,20]. Although via the capsaicin-like sympathetic stimulation of evodiamine, an anti-obesity effect of herbal evodia could be reasonably anticipated, evidence is not sufficient at the present time. Only Kobayashi reported that evodiamine prevented perivisceral fat accumulation and body weight increase through the enhancement of lipolysis [6]. In the present study, evodia, contrary to the author's belief, failed to prove a weight-reducing effect or an RMR-promoting effect. Despite the fact that the weight was decreased in weeks 4 and 8 when compared with the baseline in the evodia group, there was no significant difference from the placebo group.

The safety of herbal ephedra is still extremely controversial. When compared with other herbal products such as ginkgo biloba and ginseng, using ephedra proved to be more risky in Bent's study [12]. A number of anecdotal adverse events possibly due to ephedra supplements led the FDA to ban the sale of dietary supplements containing ephedra [21] while regulation is more relaxed by far in the EU [4]. Several clinical studies support the safety of ephedra [22–24]. Greenway reported ephedra was safe both in the herbal and pharmaceutical forms mixed with caffeine [22].

In the present study, no renal or hepatic adverse effect was found in the serum test after 8 weeks of experimenting with either herb. Instead, triglyceride and total cholesterol were significantly decreased in the ephedra group after 8 weeks, which is probably due to significant weight reduction.

The result of adverse events in the present study was also not different from those of previous studies. Compared with the placebo group, the ephedra group expressed several increased complaints such as dry mouth, nausea and vomiting, insomnia and anorexia, which are stereotypes of sympathomimetic effects of ephedra. However, none of the adverse events were severe to the extent of cessation of the experiment, except in one case of nausea in the placebo group. However headaches and dull head symptoms were improved after the 8-week diet, seemingly due in part to weight loss. In the evodia group, although several adverse events happened, none of them seem to have been significant. Because the number of cases of adverse events were insufficient, statistical analysis was not performed.

Our study had several limitations. More than half the volunteers dropped out unexpectedly. Many of them abandoned the experiment due to a failure to maintain the low-calorie diet. More frequent visits to the clinic or telephone counseling may be the answer in the future. A more variable dose of herbs should be tried. We needed to evaluate dose-dependent effects of both herbs. Furthermore, statistically we didn't use an Intention-to-Treat method, which was standard for efficacy measurement. However, as the major outcomes from this study are mainly negative, we consider the alteration of statistical analysis would not change the principal results.

We conclude that both herbs' effects on the alteration of RMR were less significant than expected although ephedra with a low-calorie diet was effective in reducing weight. RMR decrease in a low-calorie diet seems to be self-limiting when the diet is lengthened. RMR change seems to be affected by constitution and body composition rather than by medicine. Ephedra and evodia were proved to be safe for short-term use in herbal form.

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References

1. Astrup A, Gotzsche PC, van de Werken K, Ranneries C, Toubro S, Raben A, Buemann B. Meta-analysis of resting metabolic rate in formerly obese subjects. *Am J Clin Nutr* 1999;69:1117–22.
2. Heymsfield SB, Allison DB, Vasselli JR, Pietrobelli A, Greenfield D, Nunez C. Garcinia cambogia (hydroxycitric acid) as a potential antiobesity agent: a randomized controlled trial. *JAMA* 1998;280:1596–600.
3. Boozer CN, Nasser JA, Heymsfield SB, Wang V, Chen G, Solomon JL. An herbal supplement containing Ma Huang-Guarana for weight loss: a randomized, double-blind trial. *Int J Obes Relat Metab Disord* 2001;25:316–24.

4. Rotblatt M, Ziment I. *Evidence-based herbal medicine*, 1st ed. Hanley & Belfus: Los Angeles, USA. (Korean Version) 2001:127–9.
5. Greenway FL, De Jonge L, Blanchard D, Frisard M, Smith SR. Effect of a dietary herbal supplement containing caffeine and ephedra on weight, metabolic rate, and body composition. *Obes Res* 2004;12:1152–7.
6. Kobayashi Y, Nakano Y, Kizaki M, Hoshikuma K, Yokoo Y, Kamiya T. Capsaicin-like anti-obese activities of evodiamine from fruits of Evodia rutaecarpa, a vanilloid receptor agonist. *Planta Med* 2001;67:628–33.
7. Kobayashi Y, Nakano Y, Hoshikuma K, Yokoo Y, Kamiya T. The bronchoconstrictive action of evodiamine, an indoloquinazoline alkaloid isolated from the fruits of Evodia rutaecarpa, on guinea-pig isolated bronchus: possible involvement on vanilloid receptors. *Planta Med* 2000;66:526–30.
8. Nieman DC, Trone GA, Austin MD. A new handheld device for measuring resting metabolic rate and oxygen consumption. *J Am Diet Assoc* 2003;103:588–92.
9. Ravussin E. Low resting metabolic rate as a risk factor for weight gain: role of the sympathetic nervous system. *Int J Obes Relat Metab Disord* 1995;19(Suppl 7):S8–S9.
10. Ko E, Rho S, Lee EJ, Seo YH, Cho C, Lee Y, Min BI, Shin MK, Hong MC, Bae H. Traditional Korean medicine (SCRT) modulate Th1/Th2 specific cytokine production in mice CD4+T cell. *J Ethnopharmacol* 2004;92:121–8.
11. Zachwieja JJ. Exercise as treatment for obesity. *Endocrinol Metab Clin North Am* 1996;25:965–88.
12. Bent S, Tiedt TN, Odden MC, Shlipak MG. The relative safety of ephedra compared with other herbal products. *Ann Intern Med* 2003;138:468–71.
13. Peirce A. *The American Pharmaceutical Association Practical Guide to Natural Medicines*, 1st ed. William Morrow: New York, USA, 1999:246–8.
14. Malchow-Moller A, Larsen S, Hey H, Stokholm KH, Juhl E, Quaade F. Ephedrine as an anorectic: the story of the 'Elsinore pill'. *Int J Obes* 1981;5:183–7.
15. Astrup A, Buemann B, Christensen NJ, Toubro S, Thorbek G, Victor OJ, Quaade F. The effect of ephedrine/caffeine mixture on energy expenditure and body composition in obese women. *Metabolism* 1992;41:686–8.
16. Hirsch J, Mackintosh RM, Aronne LJ. The effects of drugs used to treat obesity on the autonomic nervous system. *Obes Res* 2000;8:227–33.
17. Alger S, Larson K, Boyce VL, Seagle H, Fontvieille AM, Ferraro RT, Rising R, Ravussin E. Effect of phenylpropanolamine on energy expenditure and weight loss in overweight women. *Am J Clin Nutr* 1993;57:120–6.
18. Seagle HM, Bessesen DH, Hill JO. Effects of sibutramine on resting metabolic rate and weight loss in overweight women. *Obes Res* 1998;6:115–21.
19. Vukovich MD, Schoorman R, Heilman C, Jacob P 3rd, Benowitz NL. Caffeine-herbal ephedra combination increases resting energy expenditure, heart rate and blood pressure. *Clin Exp Pharmacol Physiol* 2005;32:47–53.
20. Shoji N, Umeyama A, Takemoto T, Kajiwara A, Ohizumi Y. Isolation of evodiamine, a powerful cardiotonic principle, from Evodia rutaecarpa Bentham(Rutaeceae). *J Pharm Sci* 1986;5:612–3.
21. Shekelle PG, Hardy ML, Morton SC, Maglione M, Mojica WA, Suttorp MJ, Rhodes SL, Jungvig L, Gagne J. Efficacy and safety of ephedra and ephedrine for weight loss and athletic performance: a meta-analysis. *JAMA* 2003;289:1537–45.
22. Greenway FL. The safety and efficacy of pharmaceutical and herbal caffeine and ephedrine use as a weight loss agent. *Obes Rev* 2001;2:199–211.
23. White LM, Gardner SF, Gurley BJ, Marx MA, Wang PL, Estes M. Pharmacokinetics and cardiovascular effects of ma-huang (Ephedra sinica) in normotensive adults. *J Clin Pharmacol* 1997;37:116–22.
24. Boozer CN, Daly PA, Homel P, Solomon JL, Blanchard D, Nasser JA, Strauss R, Meredith T. Herbal ephedra/caffeine for weight loss: a 6-month randomized safety and efficacy trial. *Int J Obes Relat Metab Disord* 2002;26:593–604.